REMARKS

Introductory Comments:

Claims 7, 9-11, 16-20 and 22-26 were examined in the Office Action under reply and stand rejected under 35 U.S.C. §103(a) and under the judicially created doctrine of obviousness-type double patenting. These rejections are believed to be overcome for reasons discussed below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. §101; 35 U.S.C. §112, first and second paragraphs; as well as the rejection of claims 1-11 and 29 under 35 U.S.C. §103(a) over PCT Publication WO 01/47551 to Houghton et al. ("Houghton") and Choo et al., *Proc. Natl. Acad. Sci. USA* (88:2451-2455 ("Choo"); the rejection of claims 1, 3, 7, 9, 11 and 29 under 35 U.S.C. §103(a) over PCT Publication WO 96/20698 to Levy et al., in combination with U.S. Patent No. 6,121,020 to Selby et al.; Felgner et al., *J. Biol. Chem.* (1994) 269:2550-2561; and Liu et al. *Pharm. Res.* (1996) 13:1856-1860; and the rejection of claims

Overview of the Foregoing Amendments:

Independent claims 7 and 20 have been amended to recite that the second administration is done parenterally. Support for this amendment can be found throughout the specification at, for example, page 50, lines 24-28 and in the examples.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the unamended claims.

35 U.S.C. §103(a)

Claims 7-11, 16-20 and 22-26 were rejected as being unpatentable over Houghton and Choo, and further in view of U.S. Patent No. 6,210,663 to Ertl. The Office maintains this rejection, arguing that applicants have attacked the references individually. Moreover, the Office argues Ertl "suggests the general applicability of the suggested prime/boost methodology" and "it

would have been obvious to those of ordinary skill in the art to have applied it to the induction of an immune response against the E1E2 antigens suggested by Houghton and Choo." Office Action, pages 5-6, bridging paragraph. However, applicants submit the Office has failed to present a *prima facie* case of obviousness.

First, applicants did not attack the references individually as asserted by the Examiner. Rather, applicants pointed out the elements missing from the combination as a whole, namely, the fact that none of the references suggested alone or in combination that the use of two compositions as claimed could serve to stimulate an immune response. To reiterate, there is no recognition that the use of an HCV E1E2 polynucleotide encoding amino acids 192-809 of the HCV polyprotein described by Houghton, with the subsequent administration of the E1E2 polypeptide, would in fact elicit an immune response as claimed. Neither of Choo or Ertl provide evidence that such would be the case. Choo merely describes the sequence of the HCV genome, but does not even identify the individual E1 and E2 proteins, let alone describe E1E2 complexes or even hint at the use of such complexes in a composition, and certainly does not pertain to the use of a polynucleotide encoding an E1E2 complex as claimed with the subsequent administration of an E1E2 polypeptide.

The fact that Ertl does not pertain to HCV is significant and not inconsequential as suggested by the Office. It is simply unpredictable whether a system used for one pathogen will provide protection against another pathogen. Those skilled in the art of vaccine formulation are well aware that the efficacy of a vaccine is highly dependent on the particular components, carriers and adjuvants used. None of Ertl's examples, many of which are prophetic, pertains to an embodiment where a protein boost is administered. Rather, in all of Ertl's examples, an adenovirus vector encoding the gene of interest is subsequently administered.

Additionally, Ertl is directed to methods of enhancing mucosal immunity by administering a DNA vaccine composition and subsequently administering **via a mucosal route**, i.e., intranasally, a boosting vaccine composition. See, e.g., column 2, line 55 to column 3, line 4; and column 7, lines 46-64, of Ertl. Modifying the method of Ertl, using the E1E2 antigen, as suggested by the Examiner, simply would not result in the presently claimed invention which relies on parenteral delivery of the protein boost. Indeed, the obviousness rejection is untenable

for the simple reason that modifying the cited art as proposed would completely change the function of Ertl, which is to stimulate a mucosal immune response, particularly in the vaginal mucosa (see, column 7, lines 49-50 of Ertl), and this is accomplished by mucosal delivery. As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ2d 1385 (2007) and Patent Office Guidelines regarding obviousness, an obviousness rejection is only proper when the proposed combination of elements can be made without changing the function of the method disclosed in the references (see, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007):

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one or ordinary skill in the art at the time of the invention.

Thus, an obviousness rejection is improper where the proposed modification would destroy the intended function of the reference (see, e.g. *In re Fritch* 23 USPQ2d 1780, 1783, n.12 (Fed. Cir. 1992) and *In re Ratti* 123 USPQ 349, 352 (CCPA 1979)):

> A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.
>
> [I]t would require a substantial reconstruction and redesign of the elements shown in [a cited reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate.

It remains the case that there is no combination of the cited references that teaches or suggests these methods. As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ2d 1385, 1397 (2007) an obviousness inquiry is fact-dependent and "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 82 UPSQ2d at 1389. Rather, the Supreme Court was clear that the combination of references must show that the claimed invention is a predictable combination of elements based on their known functions. The Office

has failed in this regard.

Based on the foregoing, applicants submit that the claims are indeed patentable over the cited combination. Accordingly, withdrawal of this basis for rejection is respectfully requested.

Double Patenting

Claims 7, 9-11, 16-20 and 22-26 were rejected on the ground of obviousness-type double patenting as follows:

(1) Claims 7, 9-11, 16-20 and 22-26 were rejected over claims 1-43 of U.S. Patent No. 7,329,408 in view of the teachings of Houghton, Choo and Ertl. Applicants respectfully traverse this rejection.

In particular, all of the claims of the '408 patent pertain to methods using truncated E2 molecules. The C-terminus of full-length E2 is found at amino acid position 746, numbered relative to the full-length HCV-1 polyprotein. The present claims clearly contemplate the use of a full-length E2 molecule. Thus, the claims of the instant application are believed to be patentably distinct from those of the '408 patent. Withdrawal of this basis for rejection is therefore respectfully requested.

(2) Claims 7, 9-11, 16-20 and 22-26 were provisionally rejected over claims 34-42 and 62-76 of copending application no. 10/775,964 in view of the teachings of Houghton, Choo and Ertl. Applicants respectfully traverse.

All of the claims pending in the '964 application relate to methods of **producing** microparticle compositions, not to methods of **using** the compositions as claimed in the instant application. The Examiner, himself, in the Restriction Requirement in the present application, dated April 6, 2009, required election between claims directed to methods of use as currently claimed (Group I) and claims directed to methods of making compositions (Group II). Thus, the Examiner recognizes that methods of production are separately patentable from methods of use. Accordingly, withdrawal of the double patenting rejection over the '964 application is respectfully requested.

(3) Claims 7, 9-11, 16-20 and 22-26 were provisionally rejected over claims 1-3, 5, 6, 9, 10, 12, 13, 15-17, 23, 26-28, 32-35, 37-39, 42-48, 52, 54-57, 61, 63, 64, 69, 76, 77, 79-81, 83 and

87-101 of copending application no. 10/757,708 in view of the teachings of Houghton, Choo and Ertl. Once allowable subject matter is indicated in this and/or the '708 application, depending on the claims then pending, applicants will consider the propriety of filling a Terminal Disclaimer.

(4) Claims 7, 9-11, 16-20 and 22-26 were provisionally rejected over claims 1-8, 12, 13, 15-38, 41, 45-48, 51, 52, 55-71, 76 and 77 and 62-76 of copending application no. 11/653,792 in view of the teachings of Houghton, Choo and Ertl. Applicants respectfully traverse this rejection.

In particular, all of the claims pending in the '792 application are directed to embodiments using microparticles with an ELVIS vector adsorbed thereto, wherein the vector encodes either an HIV antigen or influenza A hemagglutin antigen (see, the Amendment filed April 5, 2010 in the '792 application). All of applicants' claims, on the other hand, pertain to the use of HCV E1E2. Thus, the rejection over the '792 application should be withdrawn.

(5) Claims 7, 9-11, 16-20 and 22-26 were provisionally rejected over claims 1-15 of copending application no. 12/231,351 in view of the teachings of Houghton, Choo and Ertl. Applicants respectfully traverse this rejection.

Claims 1-6 of the '351 application all pertain to single compositions that include **both** a fusion protein with NS3, NS4, NS5a and NS5b polypeptides, and optionally a core polypeptide, **and** a polynucleotide encoding an HCV E1E2 complex. Similarly, claims 7-10 of the '351 application pertain to single compositions that include all of an NS3, NS4, NS5a, NS5b and core polypeptide **and** a polynucleotide encoding an HCV E1E2 complex. Hence, the polypeptides and polynucleotides are present together, in the same compositions in the '351 application. Claims 11-15 relate to methods of activating T cells of a vertebrate subject by delivery of the above-described compositions.

All of the present claims, however, are directed to delivery of **two** separate compositions and are therefore distinct from the claims of the '351 application. Accordingly, withdrawal of the rejection over the '351 application is respectfully requested.

(6) Claims 7, 9-11, 16-20 and 22-26 were provisionally rejected over claims 1-17, 22-33, 36-40 and 55-62 of copending application no. 12/087,330 in view of the teachings of Houghton, Choo and Ertl. Applicants respectfully traverse.

All of the claims pending in the '330 application relate to embodiments where a protein is first administered to a subject, followed by administration of a viral vector. This is completely inapposite to the claims pending in the present application where a polynucleotide composition is first administered, followed by delivery of a protein composition. Hence, the claims in the present application are believed to patentably distinguish over those of the '330 application and withdrawal of this basis for rejection is respectfully requested.

(7) Claims 7, 9-11, 16-20 and 22-26 were rejected over claims 1-3, 5, 6, 9-12, 15-24, 26-31, 35-44 and 46-50 of U.S. Patent No. 6,884,435 in view of the teachings of Houghton, Choo and Ertl. Applicants respectfully traverse this rejection.

All of the claims of the '435 patent are directed to microparticles comprising a polynucleotide antigen adsorbed to its surface and methods of raising an immune response using the microparticle. Claim 2 of the '435 patent recites that the microparticle also includes a biologically active macromolecule encapsulated therein. Again, this is different than applicants' claimed invention which requires the use of two **separate** composition, rather than a single composition as claimed in the '435 patent. Accordingly, withdrawal of this basis for rejection is also respectfully requested.

(8) Claims 7, 9-11, 16-20 and 22-26 were rejected over claims 1-13, 15-17, 20 and 24-51 of U.S. Patent No. 6,753,015 in view of the teachings of Houghton, Choo and Ertl. Applicants traverse.

As with the '435 patent above, the '015 patent includes claims directed to microparticles with a first biologically active macromolecule adsorbed thereto. Claim 16 of the '015 patent recites that the microparticle further comprises a second biologically active molecule. Thus, as with the '435 patent, the claims of the '015 patent do not pertain to the use of two **separate** compositions as claimed. Withdrawal of this rejection is therefore requested.

CONCLUSION

Applicants submit that the claims define a patentable invention and that a Notice of Allowance is therefore in order. If the Examiner notes any further matters which may be resolved by a telephone interview, the Examiner is encouraged to contact the undersigned by telephone at 650-493-3400.

Respectfully submitted,

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